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Mesocorticolimbic connectivity and motivational sensitivity: sex-specific effects of puberty in early adolescence

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Puberty demarcates the start of adolescence, a critical period of marked changes in motivated behavior (e.g., approach, avoidance) and socio-affective processing supported by development of the mesocorticolimbic circuitry—prefrontal cortex (PFC), amygdala, and nucleus accumbens (NAcc). Puberty-related increases in psychiatric risk have been linked to alterations in mesocorticolimbic circuitry function and sensitivity to rewards and punishments. Yet, how puberty influences the development of mesocorticolimbic circuitry supporting motivational traits remains unclear. We examined resting-state functional connectivity (RSFC) in 126 adolescents, studied longitudinally (216 total scans over 2 years), assessed reward/punishment sensitivity via questionnaires, and collected multimodal measures of puberty. As hypothesized, fronto-striatal RSFC was associated with reward sensitivity, but both fronto-striatal and fronto-amygdala RSFC were linked to punishment sensitivity. Puberty moderated several associations in males but not females: weaker fronto-striatal RSFC related to higher reward sensitivity in males more advanced in pubertal maturation. Further, whereas in early puberty stages stronger fronto-striatal RSFC related to higher punishment sensitivity in males, by late puberty stages, stronger fronto-amygdala RSFC was related to higher punishment sensitivity. Testosterone levels moderated the association between anterior ventromedial PFC - NAcc RSFC and reward sensitivity such that weaker RSFC related to higher reward sensitivity in males with lower testosterone levels than expected for their age and pubertal status. These data support sex-specific puberty effects on the relationship between mesocorticolimbic circuitry connectivity and reward/punishment sensitivity. Future research is needed to determine how these findings represent markers of risk for or resilience against psychiatric disorders.

Neuropsychopharmacology; https://doi.org/10.1038/s41386-026-02378-2

INTRODUCTION

Puberty—the cascade of neuroendocrinological processes by which children become adults [1]—ushers in adolescence, a critical period of neurodevelopment [2] characterized by increases in exploration and experimentation observed across species [3, 4]. Motivated behaviors are supported by changes in functional interactions between the prefrontal cortex (PFC), nucleus accumbens (NAcc), and amygdala [5]. Influential models of neurodevelopment [6, 7] have proposed that adolescent behaviors (e.g., risk-taking, sensation/novelty-seeking) may reflect heightened subcortical activity underlying motivational and affective processes (e.g., reward responsivity, socioaffective sensitivity) relative to the less consistently engaged PFC-mediated regulatory systems. Although changing dynamics within mesocorticolimbic connections facilitate adaptive socio-affective learning [8, 9] to support increasingly complex demands important for adult independence [10], they may also confer neuropsychiatric risk during this period of development [11–13]. Puberty is thought to initiate changes in sensitivity towards and processing of salient affective stimuli (e.g., peer feedback) [14], amplifying the significance of both positive and negative events. Investigators have posited that puberty-related neurodevelopmental changes in mesocorticolimbic circuitry supporting affective stimuli processing may increase vulnerability to psychiatric conditions characterized by salience misattribution, such as anxiety or substance use disorders [15, 16]. Despite epidemiological trends for pubertal onset at earlier chronological ages [17, 18] and worsening mental health symptoms in youth [19–21], how puberty-related neurodevelopmental changes relate to transdiagnostic markers of psychopathological risk, such as processing salient affective stimuli, remains unclear.

Researchers have started investigating sensitivity to positively and negatively valenced stimuli, such as rewards and punishments, respectively [22]. One prominent model of adolescent neurodevelopment (the Triadic Model) proposes that positively valenced stimuli engage the NAcc to facilitate approach/appetitive behaviors, whereas negatively valenced stimuli engage the amygdala to facilitate avoidance/aversive behaviors [23]. In this framework, the PFC plays a regulatory role as its connections with subcortical structures (e.g., NAcc, amygdala) mature through adolescence. Empirical evidence supports this conceptualization: reward sensitivity has been associated with striatal function [24],

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Received: 26 August 2025 Revised: 12 February 2026 Accepted: 19 February 2026
Published online: 23 March 2026

whereas punishment/threat sensitivity involves amygdala circuitry [25, 26], both subcortical structures exhibiting adolescent-specific signatures [27]. Further, PFC connections that mature across adolescence down-regulate amygdala responses to threatening stimuli and striatal responses to rewarding stimuli [26, 28]. This is not to suggest that reward sensitivity is restricted to fronto-striatal circuitry and threat/punishment sensitivity to fronto-amygdala circuitry: evidence implicates amygdala circuitry in reward-related processes [29] and striatal circuitry in punishment-related processes [30, 31]. Although both the NAcc and amygdala evaluate motivationally salient stimuli, the former is linked with computing prediction errors for gains, whereas the latter is associated with prediction errors for losses [32].

Excessive sensitivity to motivationally salient stimuli might be a marker of psychiatric risk [33–35] and differ by sex following pubertal onset [15, 36]. Affective disorders, such as anxiety and depression, become nearly twice as common in adolescent females than males[1] following puberty [38–40]. These disorders often involve misattribution of affective salience, reflected by alterations in mesocorticolimbic sensitivity and responsivity [41–44]. Neurobiologically, puberty may confer neuropsychiatric risk not only via elevations in gonadal hormones—which can act directly on receptors in mesocorticolimbic structures [45, 46]—but also through changes in psychosocial dynamics. Puberty-related sexual maturation not only affects socio-affective sensitivity (e.g., sexual feelings, preoccupation with social status, budding interests in romantic relationships) [47], but also how developmental changes in adolescents' bodies are perceived by themselves, their peers, and society, potentially exacerbating existing stressors based on lived experience [48].

Recent studies have characterized puberty-related changes in mesocorticolimbic structure [49–52], function [1], and connectivity [53–57]. Using resting-state functional connectivity (RSFC), which measures how regional fluctuations in the BOLD signal co-occur across discrete brain structures while the participant is "at rest" (i.e., absent exogenous stimuli), investigators have identified significant development in NAcc and amygdala connections in adolescence [58–60]. Although preliminary studies have started documenting the effects of puberty on mesocorticolimbic RSFC patterns [54, 61], the extent to which puberty moderates how relevant mesocorticolimbic connections are linked to motivationally salient stimuli processing (e.g., sensitivity to rewards/punishments) remains unclear yet crucial for understanding sex-specific psychiatric risk. Moreover, puberty is often assessed via questionnaire measures of physical maturation, which may not capture various axes of puberty (i.e., adrenarche, gonadarche) or reflect the role of sex hormones, like testosterone, which increase during puberty [62], modulate stimuli saliency, and impact motivated (e.g., approach/avoidance) behaviors [46], possibly through effects on mesocorticolimbic connectivity [55, 63, 64].

Here, we sought to (1) characterize how mesocorticolimbic RSFC relates to reward/punishment sensitivity; (2) determine how puberty moderates these relationships in a sex-specific manner; and (3) examine how endogenous testosterone levels moderate these associations. Based on previous findings, we hypothesized that fronto-striatal RSFC would be associated with reward sensitivity and fronto-amygdala RSFC with punishment sensitivity. We expected puberty to moderate the relationship between reward sensitivity and fronto-striatal RSFC in males and between punishment sensitivity and fronto-amygdala RSFC in females, based on sex-specific rises in externalizing and internalizing symptoms during early adolescence, respectively [40, 65]. As such, we tested puberty moderation models separately in males and females. We hypothesized that testosterone would moderate these relationships based on previous work implicating it in punishment sensitivity in adolescent females via changes in fronto-amygdala connections [61] and reward sensitivity in adolescent males via changes in fronto-striatal connections [66]. Based on previous findings in adolescents [61, 67, 68], we expected that higher testosterone in females would be related to weaker fronto-amygdala RSFC and greater punishment sensitivity, whereas higher testosterone in males would be related to stronger fronto-striatal RSFC and greater reward sensitivity. To determine puberty-specific influences, we tested these hypotheses while controlling for age across analyses.

MATERIALS AND METHODS

Participants

Participants included 126 adolescents recruited from the community via online advertisements and flyers (see Table 1) who were assessed longitudinally (twice within an interval of ~2 years), totaling 216 scans. Youth self-identified as male or female (69 were assigned female at birth, hereafter "females"). Females were recruited between 10 and 12 years old and males between 11 and 13 years old based on evidence that females,

Table 1. Participant characteristics.

	Visit 1 Participants ($N = 126$)	Visit 2 Participants ($N = 94$)
Age in years		
Mean (SD)	11.84 (1.03)	13.79 (1.01)
Range	10.05–13.91	12.10–16.04
Sex, *n* (%)		
Female	69 (54.76%)	50 (53.19%)
Male	57 (45.24%)	44 (46.81%)
Race, *n* (%)		
Black/African American	35 (27.80%)	22 (23.40%)
Other	3 (2.38%)	1 (1.06%)
White	76 (60.30%)	63 (67.00%)
More than one race	7 (5.56%)	6 (6.38%)
Unknown/Not reported	1 (0.79%)	2 (2.12%)
Missing	4 (3.17%)	0 (0.00%)
Annual income (USD $), *n* (%)		
< 35,000	28 (22.22%)	13 (13.83%)
35,000–45,000	8 (6.35%)	8 (8.51%)
45,000–55,000	14 (11.10%)	7 (7.45%)
55,000–95,000	25 (19.84%)	22 (23.40%)
95,000–105,000	8 (6.35%)	9 (9.57%)
105,000–150,000	21 (16.70%)	21 (22.30%)
150,000+	14 (11.10%)	11 (11.70%)
Missing	8 (6.35%)	3 (3.19%)

Demographic categories with less than 5% endorsement at either visit were collapsed to mitigate concerns of participant identifiability. "Other" race included Native American/Alaska Native, Asian, and Native Hawaiian/Pacific Islander.

[1]Throughout, we refer to youth as 'males' and 'females' based on the parent study demarcation (for literature reviews) or based on self-identification of binary sex stemming from sex assigned at birth based on visual inspection of genitalia; however, this approach denies how biological sex operates on a continuum (e.g., testosterone is biologically active across sexes), and that for many youth, sex assigned by chromosomes, endocrine, or genitalia are not dichotomous (e.g., ovarian streaks in girls with Turner syndrome). See [37] for a discussion.

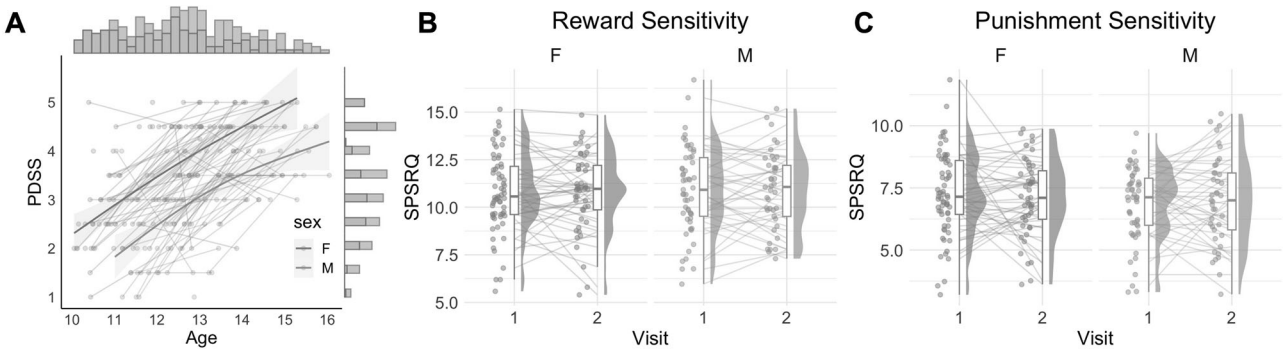

Fig. 1 Study participant characteristics, including age, pubertal status, and reward/punishment sensitivity. A Participant distributions by age, pubertal status, and sex. **B** SPSRQ scores on reward sensitivity, and **C** SPSRQ scores on punishment sensitivity. Each point reflects an individual visit, and lines connect individual participants across visits. PDSS Puberty Development Scale Score (transformed to 5-point Tanner scale), SPSRQ Sensitivity to Punishment and Sensitivity to Reward Questionnaire, F female, M male.

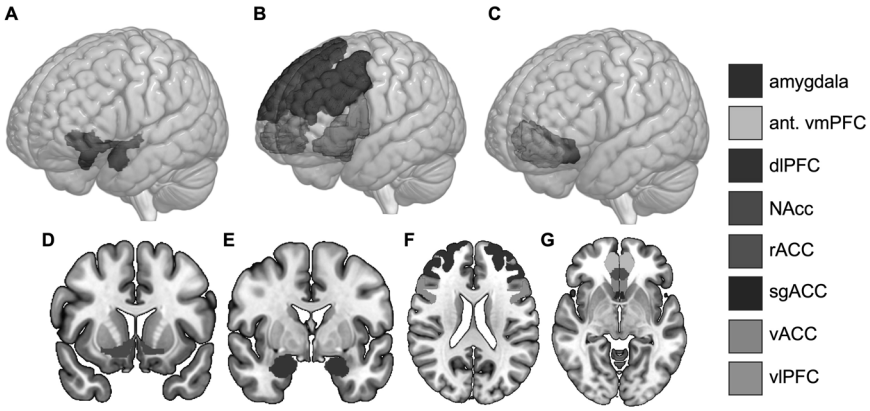

Fig. 2 Mesocorticolimbic circuitry ROIs are overlaid onto a standard brain templates (three-dimensional in top row; two dimensional in bottom row. ROIs include subcortical regions (**A**), including the NAcc (**D**) and amygdala (**E**), lateral frontal cortical ROIs (**B**, **F**), and medial frontal cortical ROIs (C, G). ROIs regions-of-interest, ant. vmPFC anterior ventromedial prefrontal cortex, dlPFC dorsolateral prefrontal cortex, vlPFC ventrolateral prefrontal cortex, rACC rostral anterior cingulate cortex, vACC ventral anterior cingulate cortex, sgACC subgenual anterior cingulate cortex, NAcc nucleus accumbens.

on average, begin puberty approximately one year earlier than males in the United States [69, 70].

Parents provided written informed consent and adolescents provided written assent prior to study enrollment. The study was approved by the University of Pittsburgh Human Research Protection Office. Participants received task performance-based earnings in addition to compensation for their participation in the larger study. Additional study details (e.g., exclusion criteria) can be found in the Supplement.

Puberty assessments

Tanner stages range from 1 ("prepubertal") to 5 ("adult-like") based on genital development in males, breast development in females, and pubic hair development in all youth [71, 72]. Tanner stage was assessed using self-report and clinical observation by a trained staff member in a medical examination room within the neuroimaging center and used to ensure a comparable range in pubertal status in males and females. Adolescents also completed the Puberty Development Scale (PDS) [73], a self-report measure of physical development. For this study, we used a composite score from the PDS self-report items, which captured the underlying process of pubertal development, including adrenal and gonadal maturation. The composite score (PDSS, transformed to scores from 1 to 5), used for our puberty analyses, was created for male and female participants.

See Fig. 1A for transformed PDSS distributions by age and sex for study participants and Supplement for additional details.

Pubertal hormonal measure

Circulating testosterone was measured using indices from Bayesian modeling of three morning salivary assays over four weeks, following well-established protocols, and standardized by sex [74]. See Supplement and previous work [63] for additional details.

Reward and punishment sensitivity assessment

Sensitivity to reward and punishment was assessed using the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) [75], which was completed by the participant's parent. The SPSRQ includes a total of 48 items comprising two subscales (24 items each): sensitivity to reward and sensitivity to punishment. See Fig. 1B, C for reward and punishment sensitivity distributions, respectively, by sex and Supplement for additional questionnaire details.

Magnetic resonance (MR) data acquisition and preprocessing

MR data were collected on a 3T Siemens Biograph mMR scanner at the Magnetic Resonance Research Center located at the University of Pittsburgh Medical Center (Pittsburgh, PA). See Supplement for information on acquisition parameters and preprocessing decisions.

Region-of-interest (ROI) selection

Regions-of-interest (ROIs) were selected a priori based on developmental neuroscience research showing mesocorticolimbic cortical-subcortical circuitry maturation during the adolescent period [54, 76, 77]. The six cortical ROIs include the anterior ventromedial prefrontal cortex (vmPFC), subgenual (sg-), rostral (r-), and ventral (v-) anterior cingulate cortices (ACC), dorsolateral prefrontal cortex (dlPFC), and ventrolateral prefrontal cortex (vlPFC). Subcortical ROIs included the amygdala and nucleus accumbens (NAcc). Figure 2 depicts ROI masks on a standard brain template. See Supplement for additional information.

Resting-state functional connectivity (RSFC)

Consistent with prior work to estimate functional connectivity [56], time series were extracted from each participant's resting-state functional images by taking the first principal component across all voxels within each ROI. Pearson correlation coefficients were computed between ROI seeds and normalized using Fisher's Z transformation.

Data analysis plan

We used linear mixed effects models for all statistical tests (lmerTest::lmer, R version 4.3.1) [78–80]. Neuroimaging (i.e., rsfMRI) and behavioral (i.e., SPSRQ) data were acquired at both timepoints. The longitudinal structure of these data (i.e., repeated measures) was included in our modeling approach. All models included a random intercept for participant ID ('id' below) to account for longitudinal data (i.e., repeated measures). Analyses focused on resting-state functional connectivity (RSFC) between six PFC ROIs and two subcortical ROIs, the amygdala and NAcc, resulting in 12 possible cortical-subcortical connections. All models included age as a covariate. We covaried for sex in models that combined males and females. Continuous variables (e.g., age, SPSRQ, PDSS) were centered prior to running models.

We tested four models to determine (1) associations between mesocorticolimbic RSFC and reward/punishment sensitivity, (2) moderation by puberty (PDSS) of significant associations identified in the first model, tested separately in males and females, (3) moderation by testosterone of significant associations identified in Model 2, and (4) moderation by testosterone of significant associations identified in Model 2 beyond total puberty effects. We tested males and females in separate models given potential puberty-related sex differences in developmental timing, hormonal mechanisms, and neurobiological effects, and to improve interpretability. Our analytic approach followed a hierarchical testing framework. That is, we first tested associations between mesocorticolimbic RSFC and reward/punishment sensitivity. For connections exhibiting significant associations following multiple comparison corrections, we tested the extent to which pubertal maturation moderated those brain-behavior relationships. This approach was motivated by our primary interest in characterizing how puberty relates to brain-behavior associations rather than testing all possible moderation effects. Model specifications are included in the Supplement. All *p*-values were FDR-corrected [81] for multiple comparisons and applied across all tested connections within each of our four models (see Supplement for details).

RESULTS

Zero-order correlations

Zero-order correlation tables for variables of interest, including age, puberty (PDSS), salivary testosterone, reward sensitivity (SPSRQ), and punishment sensitivity (SPSRQ), are presented for all participants in Supplementary Table S1A, and separately for males in Supplementary Table S1B, and females in Supplementary Table S1C.

Sensitivity to reward and punishment (*Model 1*)

Sensitivity to reward was associated with weaker RSFC between the anterior vmPFC and NAcc ($\beta = -0.19$, $p_{FDR} = 0.007$) but no other connection examined ($p_{FDR} > 0.05$). Sensitivity to punishment was associated with stronger RSFC between several fronto-striatal connections, including between the anterior vmPFC and NAcc ($\beta = 0.21$, $p_{FDR} = 0.002$), rACC and NAcc ($\beta = 0.21$, $p_{FDR} = 0.002$), vACC and NAcc ($\beta = 0.15$, $p_{FDR} = 0.029$), dlPFC and NAcc ($\beta = 0.26$, $p_{FDR} < 0.001$), and vlPFC and NAcc ($\beta = 0.20$, $p_{FDR} = 0.002$). Additionally, sensitivity to punishment was associated with stronger RSFC between several fronto-amygdala connections, including between the anterior vmPFC and amygdala ($\beta = 0.17$, $p_{FDR} = 0.012$), rACC and amygdala ($\beta = 0.15$, $p_{FDR} = 0.038$), dlPFC and amygdala ($\beta = 0.18$, $p_{FDR} = 0.007$), and vlPFC and amygdala ($\beta = 0.21$, $p_{FDR} = 0.002$) but no other connection examined ($p_{FDR} > 0.05$). See Supplementary Table S2 for model statistics for the tests above.

Moderation by pubertal status (*Model 2*)

We next sought to determine the extent to which puberty moderated the relationship between mesocorticolimbic RSFC and reward/punishment sensitivity beyond age effects. We tested these associations separately in males and females.

Male participants. Puberty moderated the relationship between anterior vmPFC – NAcc RSFC and reward sensitivity ($\beta = 0.39$, $p_{FDR} < 0.001$; Fig. 3A1). Simple slopes analyses revealed that weaker anterior vmPFC – NAcc RSFC was associated with greater reward sensitivity only from PDSS 1 to 3 but not in later stages (Supplementary Table S3B). Puberty also moderated the relationship between punishment sensitivity and RSFC in the following two fronto-striatal connections: anterior vmPFC – NAcc ($\beta = -0.24$, $p_{FDR} = 0.004$; Fig. 3B1) and vACC – NAcc ($\beta = -0.19$, $p_{FDR} = 0.022$; Fig. 3B2). Simple slopes analyses revealed stronger RSFC in both connections was associated with greater punishment sensitivity from PDSS 1 to 3 but not in later stages. Puberty further moderated the relationship between punishment sensitivity and amygdala RSFC with the rACC ($\beta = 0.24$, $p_{FDR} = 0.002$; Fig. 3B3) and vlPFC ($\beta = 0.32$, $p_{FDR} < 0.001$; Fig. 3B4): stronger RSFC in both connections was associated with greater punishment sensitivity, but only from PDSS 3 to 5 and not in earlier stages.

No other puberty moderation effects were observed in males ($p_{FDR} > 0.05$). See Supplementary Table S3A for model statistics and Fig. 3 for model plots.

Female participants. Puberty did not moderate the association between mesocorticolimbic RSFC and reward/punishment sensitivity in any connection examined in females ($p_{FDR} > 0.05$; Supplementary Table S3C).

Supplemental moderation analyses. For completeness, we performed supplemental analyses, which examined potential moderation effects of pubertal maturation across all cortical-subcortical mesocorticolimbic ROI pairs (i.e., including for connections without main effects on reward/punishment sensitivity; Supplementary Table S4A, S4B). These analyses revealed six additional associations (Supplementary Fig. S1), all in males and related to reward sensitivity, including significant pubertal moderation in the following connections: sgACC – NAcc ($p_{FDR} = 0.001$), rACC – NAcc ($p_{FDR} < 0.001$), vlPFC – NAcc ($p_{FDR} = 0.048$), anterior vmPFC – amygdala ($p_{FDR} = 0.003$), sgACC – amygdala ($p_{FDR} = 0.031$), and vACC – amygdala ($p_{FDR} = 0.012$).

Exploratory testosterone analyses (*Models 3 + 4*)

Salivary testosterone significantly moderated the relationship between anterior vmPFC – NAcc RSFC reward sensitivity in males after covarying for age effects ($\beta = 0.26$, $p_{FDR} < 0.001$) such that weaker anterior vmPFC – NAcc RSFC was most strongly associated with greater reward sensitivity in males who had lower levels of testosterone; however, testosterone did not moderate any other association between puberty-related mesocorticolimbic RSFC and reward/punishment sensitivity ($p_{FDR} > 0.05$) (Supplementary Table S5A). The moderating effect of testosterone on the relationship between anterior vmPFC – NAcc RSFC and reward sensitivity remained significant after covarying for both puberty and age ($\beta = 0.27$, $p_{FDR} < 0.001$) (Supplementary Table S5B and Fig. 3A2). No other puberty-moderated association between mesocorticolimbic RSFC and reward/punishment sensitivity was moderated by testosterone after covarying for pubertal status and age ($p_{FDR} > .05$).

Sensitivity analyses

To ensure that motion was not contributing to our primary RSFC findings, we additionally performed sensitivity analyses, which included mean FD as a covariate (following censoring of high-motion volumes). Including mean FD as a covariate did not change the significance of any association except one: after covarying for mean FD, pubertal maturation no longer moderated the relationship between punishment sensitivity and vACC – NAcc

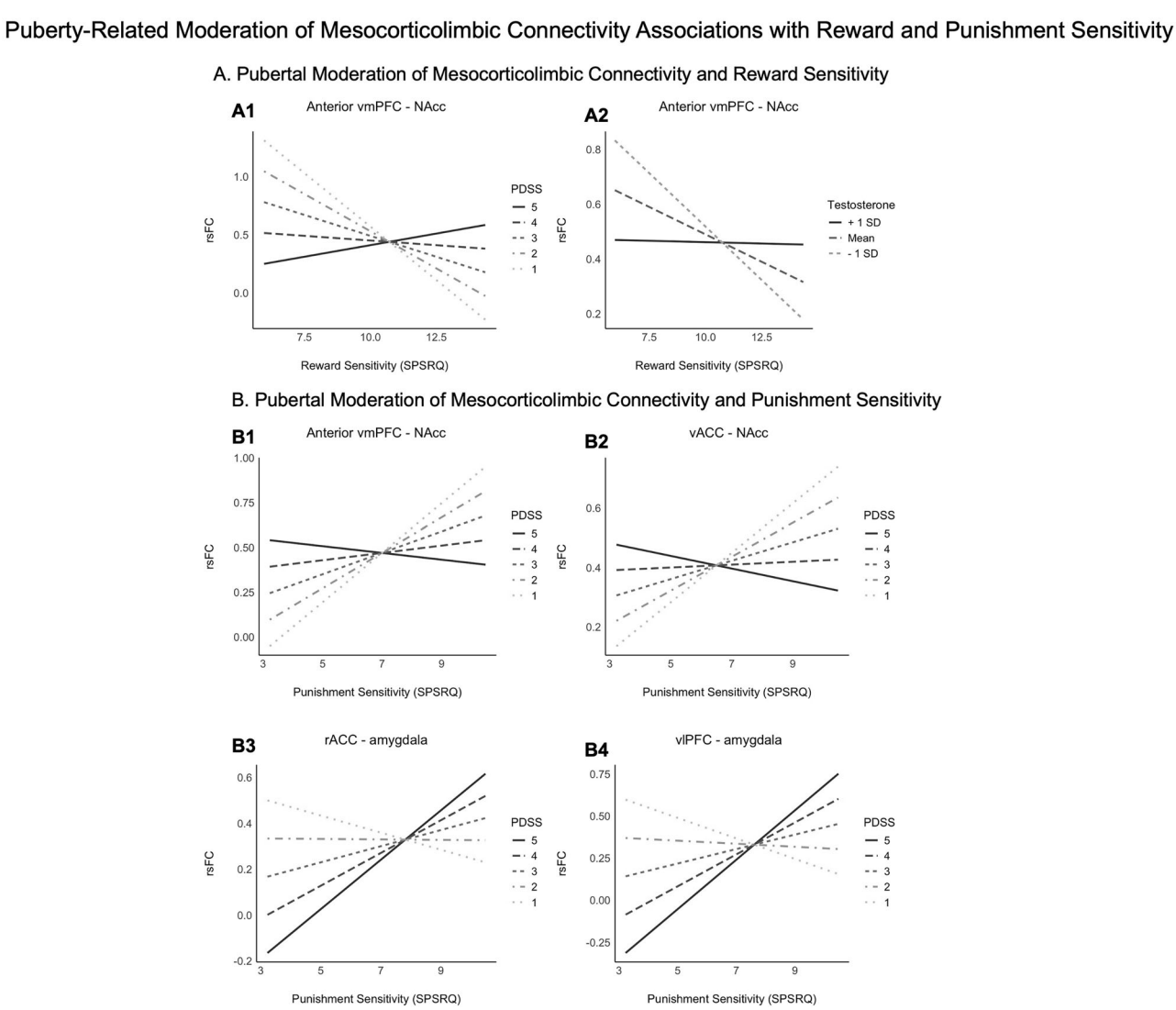

Fig. 3 Puberty, after controlling for age effects, moderates the relationship between mesocorticolimbic RSFC and motivational sensitivity in male participants. The association between reward sensitivity and anterior vmPFC – NAcc RSFC was moderated by puberty (**A**1) and basal salivary testosterone (**A**2); the association between punishment sensitivity and fronto-striatal connectivity was moderated by puberty in NAcc RSFC with the anterior vmPFC (**B**1) and vACC (**B**2); the association between punishment sensitivity and fronto-amygdala connectivity was moderated by puberty in amygdala RSFC with the rACC (**B**3) and vlPFC (**B**4). RSFC resting-state functional connectivity, PDSS Puberty Development Scale Score (transformed to 5-point scale), SPSRQ Sensitivity to Punishment and Sensitivity to Reward Questionnaire, anterior vmPFC ventromedial prefrontal cortex, NAcc nucleus accumbens, vACC ventral anterior cingulate cortex, rACC rostral anterior cingulate cortex, vlPFC ventrolateral prefrontal cortex, SD standard deviation.

RSFC in males ($p = 0.059$). Together, findings from these sensitivity analyses remained largely consistent with our initial results and suggested that head motion was not underlying our findings.

DISCUSSION

The present study provides novel evidence demonstrating (1) how mesocorticolimbic RSFC relates to reward/punishment sensitivity, (2) the sex-specific moderating effects of puberty on these relationships, and (3) how endogenous testosterone levels moderate puberty-related associations. As hypothesized, puberty moderated the association between fronto-striatal RSFC and reward sensitivity and the association between fronto-amygdala RSFC and punishment sensitivity. Significant pubertal moderation effects were observed in males only. Greater reward sensitivity in males was related to weaker anterior vmPFC – NAcc RSFC until mid-puberty (from PDSS 1 to 3). Greater punishment sensitivity in males was related to stronger fronto-striatal RSFC until mid-puberty (from PDSS 1 to 3), after which point (from PDSS 4 to 5) greater punishment sensitivity was related to stronger fronto-amygdala RSFC. After controlling for age and puberty, testosterone moderated the association between reward sensitivity and fronto-striatal RSFC, such that the association was driven by males lower in testosterone. Together, these results extend previous findings linking puberty to the emergence of sex differences in the processing of motivationally salient cues. They additionally provide neurobiological and endocrinological evidence demonstrating the importance of considering puberty to understand sex differences in psychiatric risk during adolescence.

Models of adolescent neurodevelopment and mesocorticolimbic circuitry

Consistent with the Triadic Model [23], reward sensitivity was supported by anterior vmPFC – NAcc RSFC and punishment sensitivity by fronto-amygdala connections; however, fronto-striatal RSFC was also related to punishment sensitivity, deviating

from a clear partitioning. Our finding of reward sensitivity being associated with *weaker* PFC–NAcc RSFC may reflect uncoordinated neural signaling indicative of inefficient PFC-mediated down-regulation of the NAcc. Although previous work has broadly implicated mPFC – NAcc circuitry in reward sensitivity [28], we found this to be specific to the anterior vmPFC (BA 14 m), a subregion implicated in value processing [82], reward functioning [83], and approach behaviors [84, 85], possibly via dampening of threat-related processing [86]. Reduced RSFC here may reflect weaker (e.g., immature) GABAergic inhibitory signaling from anterior vmPFC to NAcc in early adolescence, preventing cortically-mediated subcortical suppression. This may contribute to increased sensation-seeking, risk-taking, and externalizing symptoms during early adolescence. As mPFC - NAcc circuitry matures through adolescence, with the former increasingly able to effectively dampen activity in the latter, RSFC between these regions should weaken with development, consistent with recent findings [56, 87].

fMRI evidence suggests that subcortical activity is more sensitive to salient stimuli in adolescents relative to children or adults [27]. This has been interpreted to suggest that, like sensitivity to positive stimuli, sensitivity to negative stimuli (e.g., punishments) is characterized by immature and less efficient PFC-mediated amygdala downregulation, indexed by weaker RSFC being linked to greater punishment sensitivity. However, greater punishment sensitivity being related to stronger PFC RSFC with both the NAcc and amygdala suggests cortical-subcortical cooperation rather than competition when processing negative stimuli, consistent with recent work identifying distributed circuitry for threat-processing [88].

Sex differences in the role of puberty in the mesocorticolimbic circuitry – reward/punishment sensitivity relationship

After controlling for age effects, weaker anterior vmPFC – NAcc RSFC was linked to greater reward sensitivity in males less advanced in puberty, driven by males lower in testosterone. Evidence from non-human animal work shows PFC GABAergic neurons to be immature during early stages of puberty [89, 90], possibly contributing to uninhibited striatal activity resulting in heightened reward sensitivity and responsivity [91]. Our finding may speak to how less pubertally mature males exhibit developmental peaks in reward-related behaviors, such as sensation-seeking and/or risk-taking [3, 92]. These reward-related behavioral changes are present in females, though more prominent in males [93], who exhibit greater externalizing than females [94]. Although we expected fronto-striatal circuitry to support reward sensitivity, we did not expect it to also support punishment sensitivity. This finding is consistent with evidence from cross-species studies implicating the ventral striatum in processing aversive stimuli—or negative outcomes—as well as positive ones [95–99]. Interestingly, greater punishment sensitivity was related to fronto-striatal RSFC in males less advanced in puberty but with fronto-amygdala RSFC in those more pubertally mature. This could suggest that when processing aversive stimuli during early puberty, males predominantly engage structures implicated in stimuli valuation and decision-making to motivate behaviors away from potential threats [100–103]; processing aversive stimuli later in puberty, males may instead rely on structures, such as the amygdala, involved in detecting salient stimuli (e.g., threats) [104, 105] and cortical regions facilitating mature emotion regulation strategies. The vlPFC and rACC support cognitive reappraisal [106], develop through adolescence [76, 107], and dampen physiological responses in potentially aversive contexts (i.e., in the face of punishment) that activate the amygdala [108–111]. We expected higher punishment sensitivity—related but not identical to threat sensitivity—to be associated with *weaker* fronto-amygdala RSFC, reflecting ineffective PFC-mediated downregulation of amygdala activity [112]. Much like how the PFC developmentally inhibits striatal activity, it has been suggested to inhibit amygdala responses to salient cues that would otherwise prepare an organism to flee or fight [113–115]. Our finding, however, is consistent with previous work linking stronger fronto-amygdala RSFC to emotion regulation [116] and evaluation of aversive contexts or negative outcomes [117]. Coordinated fronto-amygdala signaling, as observed here in males more advanced in puberty, may be facilitated by the prolonged myelination of white matter tracts, like the uncinate fasciculus [118] and susceptible to puberty-related effects [16]. Finally, our sex-specific finding in males is consistent with work linking micro-structural alterations in the uncinate fasciculus to anxiety disorders in male but not female children [119]. Null findings in females and methodological considerations regarding testosterone measurement are discussed in the Supplement.

Strengths and limitations

Our study has several strengths, including recruiting males older than females to ensure variation in pubertal status across our sample [69, 70], characterizing pubertal maturation using multiple measures, and leveraging longitudinal neuroimaging data to observe within-person developmental changes.

Our study also has some limitations, including using parent-reported reward/punishment sensitivity and resting-state instead of task-based fMRI, rather than self-reported motivational sensitivity and measuring variability in participants' neural responses to presented stimuli (e.g., rewards, punishments) in a task paradigm. Further, our study design included 1-2 timepoints, precluding reliable estimations of pubertal tempo, or rate of change, via random slopes. We encourage future investigations into adolescent developmental trajectories to incorporate denser longitudinal data (i.e., more than 2 timepoints) to characterize inter-individual heterogeneity in pubertal maturation, trajectories that may be non-linear and better captured by additional timepoints. Our sample was also limited to individuals assigned male or female at birth, limiting generalizations in gender diverse youth [120–122]. We caution readers against extending our findings to other populations given the demographic composition, size, and community-based recruitment of our study sample. It will be crucial for future studies to recruit larger and more diverse samples (e.g., with regard to race/ethnicity, socioeconomic status, etc.) to understand the generalizability of our findings. Finally, evidence implicates additional structures beyond mesocorticolimbic regions in reward-processing, including the dorsal striatum (e.g., caudate and putamen) [123], related to puberty [54, 56], as well as others involved in punishment-processing, such as the anterior insula and periaqueductal gray [124–126].

CONCLUSION

In sum, our findings demonstrate a sex-specific role of pubertal maturation on the relationship between mesocorticolimbic RSFC and reward/punishment sensitivity. Further research is needed to characterize how puberty-specific neurodevelopmental mechanisms relating to these traits may confer risk for or promote resilience against psychiatric conditions during adolescence. Our findings have several implications for early identification and prevention of psychopathologies with adolescent onsets. Broadly, heightened reward sensitivity is a risk factor for externalizing disorders (e.g., substance use disorders) and heightened punishment sensitivity for internalizing disorders (e.g., anxiety disorders), which most often emerge during adolescence [12, 127–129]. Our finding indicating that less pubertally mature males exhibit stronger associations between fronto-striatal connectivity and reward sensitivity indicates a potential developmental period during which preventative interventions targeting reward-related behaviors may be most efficacious. We additionally observed a developmental shift wherein punishment sensitivity in relatively

less pubertally mature males was related to fronto-striatal connectivity but to fronto-amygdala connectivity in those more pubertally advanced. This may suggest that the neural substrates underlying vulnerability for internalizing disorders may change across pubertal maturation. In practice, this may indicate that specific screening tools or neural biomarkers for psychopathologies may differ depending on adolescents' pubertal status. Future longitudinal studies should investigate how brain-behavior relationships may prospectively predict psychopathological risk or emergence of symptoms, including in larger datasets, such as the Adolescent Brain Cognitive Development (ABCD) Study [130, 131]. Taken together, evidence from the present study indicates that how mesocorticolimbic function relates to reward/punishment sensitivity varies with puberty in a sex-specific manner, deepening our nascent but burgeoning understanding of neurodevelopmental processes underlying psychiatric risk and resilience.

DATA AVAILABILITY

Deidentified data from this study will be made available by the lead author upon reasonable request.

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ACKNOWLEDGEMENTS

The study authors would like to thank the study participants, their families, and the research staff in the Cognitive-Affective Neuroscience & Development (CAN-D) Lab for making this work possible.

AUTHOR CONTRIBUTIONS

AO and CDL designed the study; AO led data processing and analysis, and writing; TRH, NPJ, and EAS assisted with data processing and analysis. All authors contributed to interpretation, writing, and approving the final manuscript.

FUNDING

This research was supported by grants from the National Institute of Mental Health (R01MH099007, PI: Ladouceur).

COMPETING INTERESTS

The authors declare competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41386-026-02378-2.

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